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Autologous hematopoietic stem cell transplantation for autoimmune disease – is it now ready for prime time?

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Abstract

Current systemic therapies are rarely curative for patients with severe life-threatening forms of autoimmune disease (AID). During the past 15 years autologous hematopoietic cell transplantation (HCT) has been demonstrated to cure some patients with severe AID refractory to all other available therapies and thus AID has become an emerging indication for cell therapy. The sustained clinical effects after autologous HCT are better explained by qualitative change in the reconstituted immune repertoire rather than transient depletion of immune cells. Since 1996, more than 1300 AID patients have been registered by the European Group for Blood and Marrow Transplantion (EBMT) and almost 500 patients by the Center for International Blood and marrow Transplant Research (CIBMTR). Autologous HCT is most common performed for patients with multiple sclerosis (MS) or systemic sclerosis (SSc). Systemic lupus, Crohn's disease, type I diabetes, juvenile idiopathic arthritis are other common indications. Allogeneic transplants are still considered too toxic for use in AID except for cases of immune cytopenia. While biologic therapies have been effective at controlling the manifestations of the disease they require continuous administration, thus raising questions about their increasing costs, morbidity and mortality related to prolonged therapy. Perhaps it is a reasonable time to ask, "Is autologous HCT for severe AID now ready from prime time?" Yet, the paucity of controlled studies, the short-term toxicities and the upcoming availability of second-generation biologic and target immunotherapies, argues that perhaps HCT for AID should be limited to clinical trials. In this article we focus on the results of autologous HCT for MS and SSc as these are two most

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commonly transplanted diseases. The promising data that is emerging may establish these diseases as standard indications for HCT.

Keywords

Hematopoietic stem cell transplantation; autoimmune disease; multiple sclerosis; systemic sclerosis

INTRODUCTION

Autoimmune diseases (AID) affect about 5% of the population. Current systemic therapies are rarely curative for those patients with the most severe, life-threatening forms of AID. During the past 15 years, based on the experience from experimental models and early clinical trials, hematopoietic cell transplantation (HCT) has become an emerging indication for cell therapy. The use of HCT for AID has been comprehensively reviewed [1]. Durable, progression-free survivals in the range of approximately 50% are now reported for patients who have failed multiple therapies. Concurrently there has been a significant improvement in the safety of autologous HCT [2]. The sustained clinical effects of autologous HCT for AID are best explained by qualitative change in the reconstituted immune repertoire rather than transient depletion of immune cells, supporting a hypothesis that there is a “resetting” of the immune system [1]. Since 1996, more than 1300 AID patients have been registered by the European Group for Blood and Marrow Transplantion (EBMT) and almost 500 patients by the Center for International Blood and marrow Transplant Research (CIBMTR) [3]. Autologous HCT is most common performed for patients with multiple sclerosis (MS) or systemic sclerosis (SSc). Systemic lupus, Crohn’s disease, type I diabetes, juvenile idiopathic arthritis are other common indications. The majority of these HCT (~90%) are autologous procedures as allogeneic HCT is still considered too toxic for use in AID except for cases of immune cytopenias.

While biologic therapies have been effective at controlling the manifestations of the disease they require continuous administration, thus raising questions about their increasing costs, morbidity and mortality related to prolonged therapy [4]. Thus, the prospect of developing a therapeutic option using a one-time intervention with the potential of durable or curative treatment-free survival is attractive. Given the alternatives perhaps it is a reasonable time to ask, “Is autologous HCT for severe AID now ready from prime time?” Some argue that given the paucity of controlled studies, the short-term toxicities and the upcoming availability of second-generation biologic and target immunotherapies, HCT for AID should be limited to clinical trials. Here, we focus solely on results of autologous HCT for MS and SSc as these are two most commonly transplanted AID. The promising data emerging from clinical trials may turn the tide in the near future and establish AID on the list of standard indications for HCT.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is an inflammatory demyelinating and degenerative disease of the central nervous system with heterogeneous clinical features and a diverse long term prognosis. Relapsing-remitting (RR) MS is the result of recurrent localized acute inflammation in the CNS while secondary progressive (SP) MS is an on-going neurodegenerative state resulting from the accumulated damage caused by the earlier recurrent inflammatory events. Occasionally, patients present with a progressive form of MS (PP-MS) without a preceding RR phase. Interferon-β and Glatiramer acetate are most frequently used as a first-line treatment for RRMS. Patients who continue to experience relapses or begin to develop progressive disabilities are often switched to other agents such as Natalizumab, Fingolimod, Mitoxantrone or Cyclophosphamide. Several new drugs for treating MS are in late stage clinical trials and may provide new alternatives for some patients with RRMS. Mitoxantrone, has been shown to temporarily halt or slow the tempo of progressive disabilities during SPMS.

Intensive immunosuppressive schemes have been proposed as “salvage” therapy for some patients who continue to deteriorate after these conventional treatments. Pilot studies began in the 1990s and provided the proof of principle that HCT could induce stabilization in patients with severe MS. The HCT conditioning regimen used for MS eliminates the existing immune system that harbours disease-associated cells. A new and healthy immune system regenerates from immature hematopoietic progenitor cells [5]. Immunological studies have corroborated this notion by linking the reduction of MS inflammatory events to an extensive renewal of the adaptive immune system following HCT, in which the T cell pool is gradually repopulated by thymus-derived naïve cells [6].

Due to its risk profile, immunodepletion followed by autologous HCT has been limited to patients with highly active, rapidly deteriorating, treatment refractory forms of MS. Registry data have documented at least 400 patients have undergone autologous HCT for treatment of severe MS, either as part of a clinical trial or under local protocols [7]. Heterogeneous patient populations and transplantation regimens, small number of patients, and lack of a control arm reduce the quality of evidence that can be inferred from these data. With this caveat in mind, there is data available that provides support for further exploration of the role of HCT in MS. Suppression of relapses and of Gadolinium-enhancing MRI lesions after HSCT has been clearly demonstrated [8–10]. Indeed, no other treatment has shown such a degree of suppression of new MRI lesions in the absence of any maintenance treatment [7]. However, as most trials of HCT in MS, until recently, enrolled predominantly patients with progressive forms (PP or SP), relapse rates are of limited usefulness as an outcome measure for the evaluation of efficacy. For this reason, as well as for its greater impact on patients’ quality of life, disability is considered a more relevant outcome measure. The largest data set currently available is a retrospective analysis of data from 178 patients reported to the EBMT Registry, last updated in 2006 [11]. The analysis reported a progression-free survival in 60–70% of patients after 3 years and 50–60% after 6–8 years. More recent original reports have shown a progression-free survival that was disappointingly low (36%) in a

single study with 3 year follow-up but ranged from 70 to 100% after varying duration of follow-up (1.5–6 years) in all other reports. Where extended follow-up of the patients was available, gradual resumption of progression has been observed over time [11–13].

The continued worsening of disability after HCT has been associated with pre-existing chronic, severe disability (EDSS 6.0 and above) prior to HCT. More durable remissions and in some cases improvement of neurological function is seen for subjects with less advanced disability (EDSS ≤6) and for patients in the RR phase prior to HCT [14–15]. Burt et al recently treated 21 RRMS patients with mild to moderate disability (EDSS 2.0–5.5) with a reduced-intensity conditioning HCT regimen and reported 100% progression-free survival, with 81% showing an improvement of neurological function after a median of 3 years of follow-up [16]. However, 25% of patients experienced MS relapse following HCT, which was higher than what was previously observed in intermediate- and high-intensity regimes. Similarly, Krasulova and colleagues recently described a case series treated in Prague and reported significantly higher rate of progression-free survival in RR than in SPMS patients. This report also confirmed an association of a better clinical outcomes in patients with short disease duration (<5 years from diagnosis) and a younger age, the latter in agreement with the EBMT report [12] and the experience from a Russian case series [17]. Long-term follow up data from a larger number of patients is needed to document and refine appropriate inclusion criteria and is the purpose of a recently activated cooperative EBMT and CIBMTR study.

Young patients with highly aggressive, rapidly evolving (malignant) forms of MS are a group that seems to especially benefit from HCT. These forms have been termed “malignant” because of their poor prognosis [18–19]. Case reports have described dramatic clinical improvement, stabilisation of lesion burden, and suppression of relapses in patients with highly active RRMS that had experienced high numbers of relapses [20]. In a recent report by Fagius and colleagues on 9 patients treated with HCT as rescue/salvage therapy for malignant RRMS, the relapse rate dropped from 61 in 82 patient/months before HCT to one in 289 patient/months following HCT; no enhancing lesions were detected during follow-up in two-thirds of the patients, and most importantly disability was stabilized or improved in all patients with some impressive functional recoveries [18].

Can this information be translated into practice?

Patient Selection

The conditioning regimen is administered with the goal of attenuating or abolishing the destructive autoimmunity in MS patients. Thus, patients candidates for autologous HCT should have evidence of inflammatory activity (ongoing relapses or activity on MRI) to be considered for HCT. Indeed, those patients with the most active MS, often referred to as malignant MS, seem to have the clearest benefit from SCT. Patients with advanced disabilities, especially those with PPMS or SPMS that accumulate disabilities without clear inflammatory activity are less likely to benefit from HCT as the disabilities result from a neurodegenerative process rather than acute CNS inflammation. This is particularly true of those patients with an Expanded Disability Status Scale (EDSS) score of 6.5 or more. These patients require bilateral aids to maintain mobility and are only able to walk for about 20 m

without rest and tend to have ongoing progression after HCT. HCT should be considered for patients following careful selection in collaboration with a neurologist that specializes in the care and treatment of MS.

There is less data available to guide the selection of patients with variants of MS, such as Neuromyelitis Optica (NMO), for HCT. This variant is characterized by autoantibodies against aquaporin 4, relapses manifesting as optic neuritis and transverse myelitis, and the rapid development of severe visual impairment and severe restrictions on mobility. HCT is being explored as a novel treatment strategy given the severity of the disabilities and the poor outcome with standard immune suppressive.

Pre-transplant Evaluation

The patient should be thoroughly evaluated by an MS specialist prior to HCT. The information that should be documented in the transplant team's documentation include: whether there is a familial or genetic predisposition to MS, the frequency, severity and consequences of relapses, the patient's prior drug therapy, the current disabilities and their severity. Furthermore, if a recent MRI is not available, it should be performed prior to HCT to serve as a baseline for future follow-up.

The Multiple Sclerosis Pre-HCT data form serves as a useful tool to record MS specific information [22]. This form has been developed by a group of neurologists and transplant physicians familiar with HCT for MS and has been harmonized between the EBMT Autoimmune Diseases Working Party and the CIBMTR Autoimmune Diseases Working Committee. This core set of information provides a baseline against which response to HCT can be judged.

Treatment

The two most commonly used stem cell mobilization regimens are G-CSF administered concurrently with steroids and cyclophosphamide followed by G-CSF. G-CSF may induce an MS relapse [15,23], this can be prevented by concurrent steroid or chemotherapy administration.

Cyclophosphamide mobilized grafts have a lower immune cell load which reduces the reintroduction of autoreactive cells into the recipient during transplantation. The Canadian MS study has used ex vivo immunomagnetic CD34 cell selection to rigorously deplete the graft products of immune cells to prevent reintroduction of autoreactive cells.

Different centers have explored the use of conditioning regimens with varying immune- and myeloablative intensity. A common low intensity regimen is composed of cyclophosphamide given in combination with a lymphocyte depleting antibody such as anti-thymocyte globulin (ATG) [16]. More intensive regimens include BEAM with ATG [11] or busulfan (BU) with cyclophosphamide (CTX) and ATG [24]. While low intensity regimen may reduce complication, higher intensity regimens may offer better long term control of MS.

Mortality

The high risk of serious adverse events, including death, tempered the development of HCT as treatment for MS. However, there are clear signals that risks related to HCT can be reduced. In a recent analysis of all the European cases registered in EBMT database (n =338), treatment related mortality (TRM) was 3.3% [7]. However, TRM decreased from 7.3% in 1995–2000 to 1.3% in 2001–2007. The data suggests that increased experience including more appropriate patient selection has led to improved safety. MS itself does not appear to increase the risk of HCT related mortality.

Other Complications during Mobilization, Collection and transplant

MS patients considered for HCT tend to be young to middle age adults with few comorbidities. MS patients undergoing HCT experience the expected complications at roughly the same frequency as patients undergoing autologous HCT for lymphoma. Intensive conditioning regimens and graft lymphocyte depletion may present greater risk of toxicities and infectious complications [21]. Low-intensity treatments with minimal myelosuppressive effects have been proposed in order to reduce the toxicity of the conditioning regimen [14] but may be less effective.

A few complications occur more frequently or are unique to the MS transplant recipients. Urinary tract infections are common because of the regularity of bladder dysfunction in the MS population and a frequent need for bladder catheterization, for instance to prevent hemorrhagic cystitis during cyclophosphamide administration. Febrile neutropenia and infections may precipitate a pseudorelapse, causing transient worsening of the MS symptoms and disabilities. Awareness may minimize extraneous tests, avoid inadvertent pulse steroid treatment and allow the transplant team to reassure the patient. MS patients, usually those with a greater degree of disability prior to transplantation, are at risk of developing further loss of mobility due to the chemotherapy induced cachexia and myopathy. Access to physiotherapy during the HCT admission may mitigate this problem although some patients require transfer to a specialized rehabilitation unit to foster the recovery from the worsened disabilities. Recipients of CD34 selected grafts treated with anti-thymocyte globulin are at risk for a spectrum of herpes virus reactivations including shingles, EBV lymphoproliferation [25], HHV-6 and CMV viremia. Active surveillance and/or antiviral prophylaxis are warranted.

Autoimmune phenomena not related to MS may occur in the late post-transplant period. These may be related to the use of lymphocyte depleting antibodies given in the conditioning regimen. Autoimmune thyroid disease has been seen in almost 20% of the patients at our center. Autoimmune cytopenias, predominantly ITP may also occur up to several years post-transplant [26].

Post-transplant evaluations

The patient should be thoroughly evaluated every 6 to 12 months following HCT by an MS specialist to monitor for any evidence of relapses, deterioration in pre-existing disabilities or the development of new disabilities. An annual MRI is felt to be warranted in the

longitudinal follow-up of the patient. The Multiple Sclerosis Post-HSCT data form serves as a useful tool to record this MS specific information [22].

Ongoing and future trials

At present it remains unclear which conditioning regimen offers optimal risk/benefit ratio. A study of non-myeloablative hematopoietic transplantation (ClinicalTrials.gov Identifier: NCT00273364) versus approved standard of care (i.e. interferon, copaxone, or mitoxantrone) is currently active and open to recruitment at Northwestern University, Chicago, IL. Three trials have recently been completed or closed for recruitment and the results are pending: (i) the Canadian MSBMT trial, utilizing a conditioning regimen busulphan, cyclophosphamide and ATG conditioning regimen; (ii) the randomized phase II Autologous Stem cell Transplantation International Multiple Sclerosis Trial (ASTIMS) in which the transplantation arm consisted of BEAM-ATG using an unmanipulated autologous stem cell graft collected after mobilization with cyclophosphamide compared to a control arm receiving mitoxantrone (www.astims.org) (iii) the multicentre US Phase 2 trial High-dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT MS; ClinicalTrials.gov Identifier: NCT00288626; URL: www.halt-ms.org) utilising BEAM-ATG followed by transplantation of a CD34 selected stem cell graft collected using G-CSF and steroids.

European and North American investigators are currently developing a larger multicentre randomized controlled Phase III trial. This trial will assess the safety and efficacy of autologous HSCT vs. standard of care in highly active, treatment refractory RRMS. The details of inclusion criteria, treatment regimen, and outcome measures have been summarised in a consensus report (Saccardi et al. submitted). This controlled trial will likely finally provide the evidence required to establish the role of HCT for treatment of severe, active forms of MS.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a rare, heterogeneous disease with a spectrum of clinical manifestations with vasculopathy, inflammation, fibrosis and laboratory features of autoimmunity. SSc is commonly divided in two subsets: limited cutaneous SSc and diffuse cutaneous (dc) SSc. The former is generally accepted to be more benign in its clinical features, disease course and prognosis, while the latter can be a life threatening condition. Most transplant physicians and hematologists will not routinely be involved in the care of SSc patients because this rare connective tissue disease does not normally present with hematological manifestations other than anemia of chronic disease or instances of thrombotic thrombocytopenic purpura associated with renal crisis. This may change if and when HCT becomes an accepted treatment option for selected patients suffering from severe SSc.

SSc is feared among rheumatologists and patients, for it is the most devastating connective tissue disease. Overall survival of SSc patients has improved in the past decade, due to

intensive management with the use of ACE-inhibitors to prevent ‘scleroderma renal crisis’ and immunosuppressive medication for joint involvement and interstitial lung disease. Attention to nutritional measures, smoking cessation and lifestyle interventions, (exercise therapy and physiotherapy aimed at preservation of functional ability) may also contribute to a better outlook. In spite of this, a proportion of patients with dcSSc have relentless disease progression with extensive skin involvement and visceral organ dysfunction.

Given the paucity of proven disease modifying treatments in SSc, it is not surprising that SSc was one of the first autoimmune diseases targeted with HCT. While some early case reports showed beneficial effects of autologous HCT on some disease-specific manifestations such as skin thickening, others uncovered the risks of HCT for patients with SSc. Data from registry analyses and several phase 1/2 trials confirmed that HCT is a powerful treatment modality for SSc but with significant risks for a patient [27–30]. In the early days, treatment-related mortality (TRM) of HCT ranged from 8–23% illustrating challenges facing HCT in SSc. There is a perception among specialists in the field that some non-fatal serious adverse events such as heart failure and respiratory distress syndrome occur more commonly in SSc patients that have undergone HCT. So what makes SSc patients more vulnerable to HCT related toxicity? As the name systemic sclerosis implies, SSc is characterized by generalized matrix deposition, most prominently in skin (which explains its alternative name ‘scleroderma’), but also in visceral organs (heart, lung, kidneys, gut). Heart involvement is often subclinical and may go undetected by ECG and routine cardiac echocardiography. Small vessel disease, a hallmark of SSc, may contribute to silent cardiac ischemia and patchy fibrosis leading to ventricular arrhythmia. Cardiac fibrosis can be quantified with MRI, but its utility in identifying high-risk patients remains to be demonstrated. Pulmonary arterial hypertension is a risk factor for right ventricular diastolic dysfunction explaining why SSc patients do not always tolerate hyperhydration. Prophylactic implantation of a pacemaker or ICD should be considered in selected SSc patients. Other toxicities result from lung involvement which predisposes to respiratory insufficiency from a cytokine release syndrome associated with administration of ATG or TBI, and gut involvement requiring parenteral nutrition with its attendant risks.

One might conclude that the risks of HCT in SSc are unacceptable. However, such a pessimistic interpretation of the available data may be premature. With growing experience, TRM has been dramatically reduced. This may be due to better patient selection, screening, monitoring and follow-up [2]. These factors may also partially explain the excellent results from a recent single-center controlled, open label, randomised phase 2 trial of 19 patients. HCT patients received cyclophosphamide 2 g/m^2 + G-CSF for mobilization, cyclophosphamide 200 mg/kg + rabbit ATG 6.5 mg/kg for conditioning, followed by reinfusion of unmanipulated autologous HCT. There was statistically significant improvements of the modified Rodnan skin score (a validated measure of extent of skin thickening), lung function (FVC but not DLCO) and quality of life as measured by SF-36, at 12 months for patients that underwent HCT [30]. Most control patients who crossed over to the HCT arm because of disease progression also showed benefit from HCT. Remarkably, no deaths occurred in either arm. The study was not designed to demonstrate a survival benefit and follow up was too limited to assess late effects.

Whether HCT confers a survival benefit will become clear from two on-going prospective randomised controlled phase 3 studies, the ASTIS trial and the SCOT trial, which were launched in the past decade to compare safety and long-term efficacy of HCT versus cyclophosphamde i.v. pulse therapy for patients with early dcSSc. The ASTIS trial in Europe compares autologous HCT (mobilization with cyclophosphamide 2×2 g/m^2, G-CSF, conditioning with cyclophosphamide 200 mg/kg + rabbit ATG 7.5 mg/kg, followed by reinfusion of CD34$^+$ selected autologous HCT) versus 12 monthly cycles of i.v. pulse cyclophosphamide 750 mg/m^2. With 156 patients enrolled and a median follow-up of 5 years, the first outcome data will become available in 2012. The North American SCOT trial compares mobilization with G-CSF, conditioning with cyclophosphamide 120 mg/kg, horse ATG 90 mg/kg, TBI 8 Gy with lung and kidney shielding, followed by reinfusion of CD34$^+$ selected HCT with a control arm that is almost identical to the one in the ASTIS trial. The patient eligibility criteria and outcome parameters of SCOT and ASTIS are broadly similar to allow future comparative analyses of outcome data. The results of the ASTIS and SCOT trial will yield important data on overall survival, event-free survival, disease-free survival, serious adverse events and long-term toxicity of HCT versus standard chemotherapy in a relatively high number of patients with early dcSSc. These trials will also help determine whether the benefits of HCT outweigh the risks based on a broad range of additional secondary outcome measures. As such these are the first large randomized trials in the field of autoimmune disease. A positive outcome may therefore give an impetus to further studies in other severe autoimmune diseases that are refractory to conventional therapy.

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